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Title: Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy: A prospective, placebo-controlled randomized trial (EVAPORATE): Interim Results

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EVAPORATE: NCT029226027
Aims:

Though statin therapy is known to slow coronary atherosclerosis progression and reduce cardiovascular(CV) events, significant CV risk still remains. In the REDUCE-IT study, icosapent ethyl (IPE) added to statin therapy reduced initial CV events by 25% and total CV events by 30%, but its effects on coronary atherosclerosis progression and the mechanisms of benefit have not yet been fully investigated. Therefore, this study is to determine whether IPE 4g/d will result in a greater change from baseline in plaque volume measured by serial multidetector computed tomography (MDCT) than placebo in statin-treated patients.

Methods and Results:

EVAPORATE is a randomized, double-blind, placebo-controlled trial. Patients had to have coronary atherosclerosis by coronary computed tomographic angiography CCTA (≥1 angiographic stenoses with ≥20% narrowing), on stable statin therapy with low-density lipoprotein cholesterol levels 40 to 115 mg/dl, and persistently high triglyceride levels (135-499 mg/dL). Patients underwent an interim scan at 9 months and were followed for an additional 9 months with CCTA at 0, 9 and 18 months. Here we present the protocol-specified interim efficacy results.

A total of 80 patients were enrolled, with 67 completing the 9-month visit and having interpretable CCTA at baseline and at 9-months (age=57±6 years, male=36, 63%). At the 9-month interim analysis, there was no significant change in low attenuation plaque (LAP) between active and
placebo groups (74% vs 94%, p=0.469). However, there was slowing of total non-calcified plaque (sum of LAP, fibrofatty, and fibrous plaque)(35% v. 43%, p=0.010), total plaque (non-calcified + calcified plaque)(15% v. 26%, p=0.0004), fibrous plaque (17% v. 40%, p=0.011) and calcified plaque (-1% v. 9%, p=0.001), after adjustment by baseline plaque, age, sex, diabetes, baseline triglyceride levels, and statin use.

**Conclusions:**

EVAPORATE is the first study using CCTA to evaluate the effects of IPE as an adjunct to statin therapy on atherosclerotic plaque characteristics in a high-risk CV population with persistently high TG levels. It provides important mechanistic data in regards to the reduction in CV events in the REDUCE-IT clinical trial.

**Translational Potential**

Given the robust cardiovascular event reduction seen in clinical trials of Icosapent ethyl, this study demonstrates that one potential mechanism of benefit of this therapy is to slow atherosclerosis progression. This study shows that most coronary plaque types show slowed rates of progression under the influence of statin plus Icosapent ethyl. A translational use of this information would be to potentially use this therapy in addition to statin therapy in cases with presence of significant atherosclerosis.
Introduction:

Though statin therapy has reduced cardiovascular (CV) events and slowed the progression of coronary atherosclerosis, significant CV risk remains. This residual CV risk in patients with hypertriglyceridemia on maximally-tolerated statin therapy, underscores the need for additional medical intervention. Icosapent ethyl (IPE) is an omega-3 poly-unsaturated fatty acid and assimilated into the membrane phospholipid and coronary plaques and is thought to exert beneficial effects on the pathway from plaque formation to plaque rupture. The potential effects of IPE have been ascribed to beneficial effects on improved endothelium, inflammation, oxidative stress, and platelet aggregation. IPE has been shown to improve dyslipidemia associated with atherosclerosis by reducing triglycerides without increasing low density lipoprotein cholesterol (LDL-C). These data support the plausibility that EPA can act as an anti-atherosclerosis treatment. IPE added to a statin has already been shown to reduce major coronary events by 19% in the Japan EPA Lipid Intervention Study (JELIS) of 18,645 hypercholesterolemic patients and initial CV events by 25% and total CV events by 30% in the Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT), with the mechanism(s) of benefit not yet fully understood. In a quantitative angiography trial, the Study on Prevention of Coronary Atherosclerosis Intervention with Marine Omega-3 Fatty Acids, omega-3 PUFA (both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) slowed the progression of atherosclerosis in coronary arteries. In the HEARTS (Slowing HEART Disease with Lifestyle and Omega-3 Fatty Acids) study, 285 statin patients with stable CAD were randomized to omega-3 ethyl...
ester (1.50 grams of DHA and 1.86 grams of EPA daily) or to control (no omega-3) for 30 months\textsuperscript{6} on coronary plaque types by multidetector computed tomography (MDCT) angiography. EPA and DHA did prevent the progression of fibrous plaque (p=0.018). In a prospective study, 82 acute coronary syndrome patients were randomized into three groups: Group 1 received 1.8 grams EPA/day; Group 2 received 930 mg EPA/day and 750mg DHA/day; and Group 3 received no EPA (control group). At 1 year, plaque progression by coronary computed tomographic angiography (CCTA), was found to be significantly different between all 3 groups with the lowest in the EPA groups (3.0% vs 13.8% vs 35.0% for Groups 1, 2, 3 respectively, p=0.0061).\textsuperscript{7} The objective of the Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE:NCT029226027) study is to evaluate the effects of 4 grams of IPE per day on CCTA plaque volumes in statin-treated patients with elevated triglyceride levels (135-499 mg/dL).

**Methods:**

**Study Endpoints**

The purpose of this study was to investigate whether IPE at 4 g/d, as an adjunct to diet and statin therapy, in patients with CV disease or diabetes and hypertriglyceridemia (fasting triglyceride of 135 to 499 mg/dL at randomization) effected coronary plaque progression. The primary endpoint was the change in plaque volume measured by multidetector computed tomography angiography (low attenuation plaque [LAP], then sequentially: total plaque [TP], total non-calcified plaque [TNCP], fibrofatty [FF], fibrous [F] and calcified plaque [C]. Secondary
endpoints included incident plaque rates; changes in markers of inflammation, lipids, and lipoproteins; and the relationship between these changes and plaque burden and/or plaque vulnerability.

**Study Population**

To be included, patients had to be age 30 to 85 years with known coronary atherosclerosis (narrowing of $\geq 20\%$ in 1 coronary artery by either invasive angiography or CCTA), elevated fasting triglyceride levels (135–499 mg/dL), and low-density lipoprotein levels (LDL-C) between $\geq 40$ and $\leq 115$ mg/dL. Patients had to be on stable statin therapy, with or without ezetimibe, diet, and exercise for $\geq 4$ weeks prior to study entry. All patients were instructed to maintain a low cholesterol diet and to continue on current statin therapy.

**Study Design**

The study design and rationale for EVAPORATE has been published previously. Briefly, EVAPORATE is an ongoing multi-center, randomized, double-blind, placebo-controlled trial that is evaluating the effect of IPE 4 g/day on coronary plaque progression determined by CCTA compared with mineral oil placebo. Consistent with the trial design, a total of 80 patients were enrolled, with an expected drop out of 15% of participants (including non-evaluable MDCT scans) at 3 different centers (Harbor-UCLA, Lundquist Institute, and Intermountain Health Care). Patients were randomized 1:1 to icosapent ethyl or placebo to evaluate progression rates of plaque volume on CCTA. Participants underwent an MDCT scan at baseline and then an interim scan at 9-months and are currently being followed for an additional 9-months with an MDCT scan at 18 months. We present the protocol-specified interim
efficacy as specified in our design paper and at clinicaltrials.gov (NCT029226027). The study was approved by the Institutional Review Board and was conducted in accordance with the principles of Good Clinical Practice and the trial conformed to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent before randomisation.

**Inclusion criteria included elevated triglycerides, current stable statin use, age 30-85 years of age, presence of atherosclerosis (at least a 20% stenosis in one coronary artery by MDCT angiography), diabetes and/or established cardiovascular disease.**

**Placebo Composition and Icosapent Ethyl**

Pharmaceutical grade mineral oil placebo used in EVAPORATE consisted of a purified liquid mixture of straight chain saturated hydrocarbons that meets the compendial requirements of the United States National Formulary for light mineral oil and of the European Pharmacopoeia (Ph. Eur.) for light liquid paraffin oil, chosen for its similar appearance and consistency to IPE. The placebo oil is virtually free of all aromatic hydrocarbons, unsaturated hydrocarbons, and other related impurities. The total daily dose of placebo was four 1 g soft gelatin capsules, with two capsules taken twice daily with meals.

Active treatment was using Icosapent ethyl (IPE), which is a highly purified, pharmaceutical grade, stable, ethyl ester of EPA. Icosapent ethyl is ≥96% pure as a result of multiple intermediate process steps, including distillation and chromatography.

**CT Acquisition**
After a scout radiograph of the chest (anteroposterior and lateral) had been obtained, sublingual nitroglycerin (0.4 mg) was given immediately before the contrast injection. During the CCTA acquisition, 80 mL of iodinated contrast medium (Visipaque; GE Healthcare) was injected using a triple-phase protocol: 60 mL of iodixanol, followed by 40 mL of a 50:50 mixture of iodixanol and saline, followed by a 50-mL saline flush. The 256-row scanner (REVOLUTION, General Electric, Milwaukee WI) is a volumetric device that has high-definition spatial resolution and a 16-cm detector array. The field of view (z-axis) included the mid–ascending aorta to the upper abdomen. No table movement occurred during axial volumetric scanning because of the 16 cm of z-axis coverage, and no patient required more than 16 cm of z-axis coverage. Selection of the z-axis collimation was based on the scout images demonstrating the heart size. Tube voltage was fixed at 120 kVp, to provide comparable radiation between scans. Tube current ranged from 122 to 740 mA. A medium field of view (25 cm) was selected for all patients. The gantry rotation time was 0.28 s, with a minimum temporal resolution of 140 ms. The scanner is equipped with autogating capability, which automatically adjusts HR-dependent settings.

**Coronary plaque assessment**

Quantitative plaque assessment was performed according to a previously defined protocol using semi-automated plaque analysis software (QAngioCT Research Edition Version 2.0.5; Medis Medical Imaging Systems). Based on the guidelines of the Society of Cardiovascular Computed Tomography, 17-segment coronary artery
model vessels were assessed. Only vessels greater than 1.5 mm were evaluated.

**Plaque quantification**

Plaque volume was assessed per slice in all affected coronary segments measured by semi-automated quantification software (QAngio, Medis, Netherlands). First, an automatic tree extraction algorithm was used to obtain all the 3-dimensional centerlines of the coronary tree. Based on these centerlines, straightened MPR volumes are created of all vessels. Next, the lumen border contoured and vessel wall borders were assessed using spatial first- and second-derivative gradient filters in longitudinal cross sections. Thereafter, lumen and vessel contours were detected in the individual transversal cross-sections perpendicular to the centerlines. This method is insensitive to differences in attenuation values between data sets and independent of window and level settings. Once automated software had completed the vessel trace, an expert reader manually corrected areas of misregistration. The volume of each plaque were determined by the program quantitatively and checked for proper alignment by expert reader. For each lesion, minimal lumen diameter was summed, and plaque reported as non-calcified, low attenuation, fibrous, fibrofatty or calcified. **Vessel volume was controlled for between first and follow up CT scans.** **Because scans were compared between same patient, there was no adjustment for body surface area or vessel length or size.** The protocol for quantitative plaque assessment has been widely used in numerous previous studies by the PI as well as other groups.\(^{11,12,13,14,15}\) Reproducibility was deemed excellent (R=0.99) in a similar study design by the CT core lab.\(^{16}\)

**Plaque Composition**
Plaque Composition was based upon predefined fixed intensity cutoff values of CT attenuation. These are based upon studies by comparing CCTA with virtual histology by IVUS or histological examination in our lab and others. The fixed HU cut-off values that were used for classifying were: -50 to 50 for low attenuation plaque, 51–130 for fibrofatty, 131–350 for fibrotic, and >350 for dense calcium. These values were initially based on Brodoefel et al\textsuperscript{17} and empirically optimized using three representative training sets. The inter- and intra-observer variability for the lumen and plaque volumes have been previously described.

**Planned Interim Analysis**

Using the Lan-DeMets version of the O’Brien-Fleming group sequential boundaries for a 2-look sequential design (1 interim at 9-months + final analysis), the statistical power to test the primary study endpoint was 80% based on a sample size of 70 patients randomized in a 1:1 allocation ratio and an overall experimental type I error equal to 0.05 using a 1-sided hypothesis test. If a p-value of <0.006 was achieved at 9 months then the study would be terminated because the efficacy boundary will have had been achieved. As p<0.006 was not achieved, the study is continuing. All readers, study coordinators and patients, (as well as the principal investigator) remain blinded to randomization as the trial continues to the planned 18-month endpoint.

Power Analysis:

As published in the methods paper\textsuperscript{9}, “Assuming an average of 1.7 measurable plaques per patient, with intrapatient plaque correlation of 0.24, 70 patients would provide power of 0.80 and a 1-sided type 1 error of 0.05 to detect an 8% difference
in plaque volume between the active and placebo groups.”

**Statistical Analyses**

Baseline comparisons, which included demographics, coronary risk factors, laboratory tests, and coronary plaque volume/composition, between the two arms utilized the chi-square statistic and student’s t-test and the Wilcoxon rank sum test, as appropriate. The Fisher’s exact test was used when comparing categorical variables with few data points. Results are presented as counts and frequencies (percent) for discrete variables and mean and standard deviations or median for continuous variables. Percent change in plaque between baseline and 9-months is presented as change in plaque divided by baseline plaque. Variables were evaluated for significant departures from normality (p-value <0.01 for the Shapiro-Wilk test) and homogeneity. All plaque types were found to be non-normally distributed and therefore log transformed so as to achieve a normal distribution. Univariate analysis of covariance was used to examine rates of progression between the cohorts. Multivariate analysis of covariance models were adjusted by baseline plaque, age, sex, diabetes status, and baseline triglyceride levels. All statistical analyses report 2-sided p-values for the outcomes. A p-value less than 0.048 was considered significant for the outcomes. All analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, North Carolina). All analyses were performed using intention-to-treat, with study subjects analyzed by treatment group assigned regardless of study drug adherence.

**Results:**
Population Characteristics

A total of 80 eligible subjects were enrolled, with 67 completing the 9-month visit and having interpretable CCTA at baseline and the 9-month visit. The mean age of the participants was 57±6 years with 36 being male. Table 1 shows the baseline characteristics, stratified by arm (IPE group, n=30 and placebo group, n=37) of the study participants. There were no significant differences in baseline characteristics between the groups, which included age, BMI, diabetes, hyperlipidemia, hypertension, and smoking prevalence (Table 1).

Loss to follow up is described in the CONSORT diagram for both groups. Among the IPE cohort, 2 patients are off active drug but still being followed by phone visits, 3 were lost to follow-up, 3 withdrew consent and 2 had uninterpretable scans at visit 3 (follow up). Among the placebo group, 2 patients withdrew consent and 1 is lost to follow up.

Laboratory Outcomes:

There were no significant differences in basic lipid measures of total cholesterol, LDL, HDL and triglyceride level from baseline to follow-up. Triglyceride levels did go in the direction hypothesized, with the IPE group showing an average decrease of -34.2±94.3 versus the placebo decrease of -16.1±102. (Table 2)

Efficacy Endpoints

There were no significant differences in baseline plaque characteristics between IPE and placebo groups. The most common plaque type (expressed as % of total plaque) was fibrous plaque in both IPE and placebo groups (74.7% vs. 57.9%,
respectively). However, LAP, representing the primary end point, was the least common plaque type, with only 5.1% and 6.5% of the total plaque in the IPE and placebo groups, respectively.

At the 9-month interim analysis, there was no significant change in low attenuation plaque between active and placebo groups (74% vs 94%, p=0.469) (Figure 1, Table 3). However, there was slowing of total non-calcified plaque (sum of LAP, fibrofatty, and fibrous plaque) (35% v. 43%, p=0.010), total plaque (non-calcified + calcified plaque) (15% v. 26%, p=0.0004), fibrous plaque (17% v. 40%, p=0.011) and calcified plaque (-1% v. 9%, p=0.001), after adjustment by baseline plaque, age, sex, diabetes status, baseline triglyceride levels, and statin use. Absolute values for all plaque changes are shown in Table 3. In the IPE group, there was no correlation with changes in levels of triglycerides, EPA, or hs-C reactive protein and % change in TNCP/TP/F/DC.

**DISCUSSION:**

Thus far, the EVAPORATE Study has demonstrated no significant difference in the primary endpoint of progression of coronary artery LAP volume at the interim 9-months follow-up CT examination between patients with IPE 4 g/d plus statin therapy versus statin therapy alone. While LAP was not significantly reduced at this interim endpoint, significant slowing of progression was seen with total plaque, non-calcified plaque, fibrous, and calcific plaque volumes. Of note, total plaque was slowed by 42% (p=0.0004) and non-calcified plaque by 19% (p=0.010). This trial is ongoing, and 18-month data will become available in early 2020. This builds on the prior plaque progression studies of EPA. The combination therapy with both EPA and
pitavastatin was studied using integrated backscatter intravascular ultrasonography for coronary plaque regression (CHERRY) study. This study enrolled 193 coronary patients who underwent PCI.\textsuperscript{18} Patients were randomized to pitavastatin (4 mg/day, \( n = 96 \)) or pitavastatin plus EPA (PTV 4 mg/day and EPA 1.8 g/day, \( n = 97 \)), and followed prospectively for up to 8 months. Using IVUS, both coronary plaque composition and volumes were analyzed. Lipid volume decreased from 39.2 to 34.8 (11\%) in the pitavastatin/EPA arm compared with 42.7 to 39.3 (8\%) in the pitavastatin-only arm. Thus, both the EVAPORATE and CHERRY studies showed a 19\% and 11\% plaque reduction in the EPA arms compared with placebo/open-label controls, respectively.

Ample data were acquired using coronary plaque volume in both IVUS and CCTA studies with EPA without mineral oil placebo. In the Niki study,\textsuperscript{19} statin + EPA vs statin-only with no placebo at 6 months, combination therapy reduced lipid plaque volumes significantly (18.5±1.3 to 15.0±1.5 mm\(^3\), \( p=0.007 \)) and increased fibrous volumes (22.9±0.8 to 25.6±1.1 mm\(^3\), \( p=0.01 \)) using IB-IVUS, but no significant changes were observed in the control group in any plaque volumes. Recently, a second study using IB-IVUS showed reduction in both plaque and lipid volume over 6 to 8 months in patients who were treated with 1.8 grams/day of EPA and high dose pitavastatin (4 mg/day) unlike high dose pitavastatin alone with no placebo.\textsuperscript{20} We have recently published data comparing this mineral oil placebo group from the current study to a matched cohort using cellulose based mineral oil, showing no difference in progression rates between the two studies,\textsuperscript{21} alleviating concern about the adverse effects of mineral oil as the primary difference in
progression rates between the IPE and placebo groups in this current trial.

There are only limited CCTA data regarding the effects of EPA without DHA in reducing plaque volume. Shitani et al evaluated the effects of EPA and ezetimibe on 51 lesions in 43 patients using CCTA at baseline and at 1 year and found a significant reduction in plaque in only the EPA group. In a prospective study of 82 patients with acute coronary syndrome who underwent baseline CCTA and followed for 1 year with repeat CCTA, there was significant difference in plaque progression between the 2 treatment and control groups (EPA (1.8 g/day) vs. EPA (930mg/day) + DHA (750 mg/day) vs. control: 3.0 vs. 13.8 vs. 35.0%, p=0.0061). A recent CCTA study demonstrated that high levels of EPA in the pericoronary fat were associated with a lower level of coronary inflammation, while higher pericoronary fat inflammation levels have been linked to worse CV outcomes. This provides further evidence that the anti-inflammatory properties of EPA may improve plaque progression and outcomes.

The purpose of this study was to establish a potential mechanistic assessment as to the potential benefits of EPA on atherosclerosis. Two large randomized outcome studies have demonstrated benefit with EPA when added to statin therapy. The first, which did not use a placebo, was the JELIS Trial. In JELIS, which enrolled >18,000 statin-treated Japanese patients with high cholesterol, EPA (1.8 g/d) plus statin therapy significantly resulted in the 19% relative risk reduction of coronary
events as compared to the statin monotherapy group. The second, the REDUCE-IT trial, also demonstrated MACE benefit with EPA in addition to statin therapy, with a 25% relative risk reduction in atherosclerotic events when 4 grams of IPE was added to statin therapy. This trial used the same mineral oil placebo used in the EVAPORATE study, and similar inclusion and exclusion criteria were applied in both studies.

CCTA has been successfully used in numerous studies evaluating such therapies as testosterone, statins, hormone replacement, garlic, anti-inflammatories and anti-diabetic agents. The ease of use, low cost, and minimal invasiveness makes this much more practical and desirable as a study tool for atherosclerosis than either intravascular ultrasound or carotid intimal media thickness.

EVAPORATE is the first study to evaluate coronary plaque characteristics using CCTA to evaluate IPE as an adjunct to statin therapy in a CV population with persistently high triglycerides. This study demonstrated that IPE, when added to statin therapy, was associated with slowed plaque progression compared with statin + placebo at the interim analysis. EVAPORATE provides important correlation data to understand the dramatic REDUCE-IT benefits and clinical use of IPE. Since plaque progression is associated with increased risk of CV events, slowing plaque progression is highly supportive of JELIS and REDUCE-IT, and consistent with CHERRY and related studies, demonstrating high dose EPA is associated with decreased atherosclerotic CV disease events and reduction in coronary plaque progression.
Limitations:

This study has some limitations including small sample size and short follow-up. There were also some patients that dropped out of the study and others lost to follow up, as described above. The stopping boundary for the trial was not achieved (p<0.006 in change in low attenuation plaque), most likely due to the short duration of this initial follow-up. This possibility was anticipated and therefore, only one interim analysis at half-way through the study was planned. Therefore, the study will continue for its duration of 18 months. This study duration is similar to prior prospective studies utilizing intravascular ultrasound for plaque progression, which followed patients for 18-24 months for evaluation of the primary endpoint. Another limitation of EVAPORATE is that it is not powered to adequately evaluate long-term outcomes. However, this is the first study to associate reductions in plaque volumes by CCTA (EVAPORATE Study) with improvements in outcomes (REDUCE-IT Trial) using the same study design and same intervention. Guidelines have since adapted both CT angiography as a method to identify patients at risk\textsuperscript{27,28} and icosapent ethyl as a method to reduce CV risk.\textsuperscript{29} We have performed and published extensive reproducibility work with this software and CT methodology previously documenting excellent reproducibility for noncalcified plaque volume, with ICC values well above 90% for both intra- and inter-observer reliability.\textsuperscript{16,30}

In conclusion, the ability to retard progression of atherosclerosis, as demonstrated by the EVAPORATE results, provides an important correlation by which EPA was found to provide significant benefit in both JELIS and REDUCE-IT.
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Contributions of Authors: Matthew J Budoff oversaw the study acquisition, analysis and interpretation of data, drafted the manuscript, gave final approval and is accountable for all aspects of the work. Joseph B. Muhlestein was responsible for acquisition of data and critical revision of the manuscript. Deepak L. Bhatt assisted with interpretation of data and revision of manuscript. Viet Le and Heidi may acquired data and revised the manuscript. Kashif Shaikh, Chandana Shekar and Suvasini Lakshmanan made all measurements for the study and revised the manuscript. April Kinninger performed all analysis. Sion Roy and John Tayek were both responsible for acquisition of data and critical review of the document. John R Nelson was responsible for conception and design of the study, drafting of manuscript, critical revision and final approval. All authors gave final approval of the version to be published.

**DISCLOSURES**

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board:
Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex,
Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical,
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**REFERENCES**


7 Nagahara Y, Motoyama S, Sarai M, Ito H, Kawai H, Takakuwa Y, Miyagi M, Shibata D, Takahashi H, Naruse H, Ishii J, Ozaki Y. Eicosapentaenoic acid to


Shintani Y, Kawasaki T. The Impact of a Pure-EPA Omega-3 Fatty Acid on Coronary Plaque Stabilization; A Plaque Component Analysis with 64-Slice Multi-Detector Row Computed Tomography. *J Am Coll Cardiol.* 2012; **59**: E1713

Bittner D, Goller M, Zopf Y, Achenbach S, Marwan M. High level of EPA is associated with lower perivascular coronary attenuation as measured by Coronary CTA. *J Cardiovasc Comp Tomo* 2019; **13**: S79.


ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), *European Heart Journal* 2020;41;111-188.


FIGURE LEGEND

Figure 1. Median plaque progression for each type of plaque composition measured on cardiovascular CT for the icosapent ethyl (IPE) and placebo (mineral oil) groups (IPE group, n=30 and placebo group, n=37). Univariate analysis of covariance was used to examine rates of progression between the cohorts. Multivariate analysis of covariance models were adjusted by baseline plaque, age, sex, diabetes status, and baseline triglyceride levels. All statistical analyses report 2-sided p-values for the outcomes. A p-value less than 0.048 was considered significant for the outcomes.

*Data Availability:* The data underlying this article cannot be shared publicly as the trial is ongoing and remains blinded to participants and investigators. *Once the study is concluded and finalized, the data will be shared on reasonable request to
the corresponding author.